REMARKS

1. Preliminary Matters

a. Status of the Claims

Claims 17-36 are pending in this application. Claims 18, 19, 21-28, and 33-36 are hereby canceled without prejudice to pursuing the claimed subject matter in a continuing application. Claims 17, 20, and 29-32 are amended. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the application. Upon entry of these amendments, claims 17, 20, and 29-32 will be pending and under active consideration.

b. Amendments to the Claims

Support for the amended claims can be found in the application as originally filed as shown in **Table A**.

Table A

Claim	Support
17	paragraphs 0015-0021, 0128, 354, 1959, 50911, 50912, 50918; Table 1, line 388
20	paragraphs 50905-50909; Table 1, line 388
29	paragraph 0024
30	paragraph 0024
31	paragraphs 0029, 0030, 0213
32	paragraphs 0029, 0030, 0213

c. Claim Objections

On page 4 of the Office Action, the Examiner objects to claims 21, 24, 26, and 28 because claim 21 recites plural "SEQ ID NOS." Claim 21 is canceled, thereby rendering moot the Examiner's objection.

2. Patentability Remarks

a. 35 U.S.C. §§ 101 and 112, first paragraph

On pages 4-13 of the Office Action, the Examiner rejects claims 17-36 under 35 U.S.C. § 101 because the claimed subject matter allegedly is not supported by either a specific and substantial asserted utility, a credible asserted utility or a well established utility

On page 13 of the Office Action, the Examiner asserts that because the claimed subject matter lacks substantial utility, the specification also does not provide an enabling disclosure. Applicant respectfully disagrees. In view of the claimed subject matter having credible, specific,

and substantial utility as described above, Applicant submits that the specification enables the claimed subject matter and respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, first paragraph

(1) Specific Utility

A specific utility is a utility that is specific to the particular claimed subject matter, which is in contrast to a general utility that would be applicable to a broad class of inventions. *See In re Fisher* 421 F.3d at 1371 and Guidelines. Applicant respectfully submits that the application provides a specific utility for the claimed microRNA-related nucleic acids in accordance with *In re Fisher* and the Guidelines.

In *Fisher*, the claims at issue were directed to five (5) out of more than 32,000 EST that were disclosed in the application. Each of disclosed ESTs was from a cDNA library from pooled leaf tissue of a maize plant. The Fisher application did not disclose the location of the ESTs in the genome or the function of the underlying genes. Fisher asserted that the utilities for claimed ESTs were (1) serving as a molecular marker; (2) measuring the level of mRNA in a tissue sample; (3) provide a source of primers for PCR of specific genes; (4) identifying the presence or absence of a polymorphism; (5) isolating promoters via chromosome walking; (6) controlling protein expression; and (7) locating genetic molecules of other plants and organisms. *See Id.* at 1367 and 1368. It is important to note that each of the utilities asserted were not limited to any specific gene, genetic location or protein.

The *Fisher* court concluded that the asserted utilities were clearly not "specific." The court explained that any EST transcribed from any gene in maize could perform the seven uses such as being a molecular marker, a primer, or measure the level of RNA in a tissue sample. In other words, nothing about the seven alleged uses separated the claimed ESTs from the vast number of other ESTs also disclosed in the application. The keystone to the lack of specific utility in *Fisher* is that the claimed ESTs **did not correlate to an underlying gene of known function found in the maize genome**.

Similar to *Fisher*, the current application discloses a large number of nucleic acid sequences. In stark contrast to *Fisher*, however, the instant application provides that each of the disclosed nucleic acids maybe used to target and modulate expression of **specific** gene transcripts. Table 4, lines 111-122, of the specification disclose that the **claimed microRNA-related sequences specifically target** mRNA transcripts of the Hoxb8 gene as follows:

GENE NAME	GAM SEQ-ID	TARGET	#BS	TARGET SEQ-ID	TARGET REF-ID	UTR	UTR OFFSET	TAR-BINDING-SITE-SEQ	BINDING-SITE-DRAW (UPPER:GAM;LOWER:TARGET)	SRC	GAM ACC	BS ACC	TAR ACC
GAM7553	354	HOXB8	1	19126	NP_076921.1	3	434	GTTCTCCCAACA ACATGAAACTGC CTATTCAC	C TAGGTAGTTTC TGTTGTTGGG ATCCGTCAAAG ACAACAACCC T	6	A	b	b

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                                  hsa-miR-196b  GGGUUGUUGUCCUUUGAUGGAU
                                                ||||||||||  ||||||:||||
                                  HOXB8         CCCAACAACATGAAACTGCCTA
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Consequently, the claimed nucleic acids are of a **specific and unique nature** because these nucleic acids regulate the translation of mRNAs from the **specific target gene Hoxb8**. Accordingly, the asserted utility of the claimed invention is not vague or meaningless, and there is a well-defined public benefit to regulating the Hoxb8 gene.

(2) Substantial Utility

To satisfy the "substantial" utility requirement, an asserted use must show that the claimed invention has a significant and presently available benefit to the public. *See In re Fisher* at 1371 and the Guidelines. Applicant respectfully submits that the application provides a substantial utility for the claimed microRNA-related nucleic acids in accordance with *In re Fisher* and the Guidelines.

In Fisher, it was admitted that the underlying genes for the ESTs had no known function. Fisher argued this was irrelevant because the seven asserted uses (discussed above) were not related to the function of the underlying genes. Importantly, Fisher failed to provide any evidence that any of the claimed ESTs could be used for any of the asserted uses. Consequently, the *Fisher* court concluded that the claimed ESTs were "mere 'objects of use-testing,' to wit, objects upon which scientific research could be performed with no assurance that anything useful will be discovered in the end." *See Id.* at 1373 quoting *Brenner v. Manson*, 383 U.S. 519 (1966).

In further sharp contrast to *Fisher*, the present application discloses that the claimed nucleic acids may be used to bind and regulate mRNA transcripts of Hoxb8. *See* Table 4, lines 111-122. At the time of filing, it was known in the art that Hoxb8 was a transcription factor that regulated early mouse development by providing anteroposterior axis information. *See* van den Akker *et al.*, Development, 128, 1911-1921 (2001). Furthermore, Hoxb8 was known to be transcriptionally activated in AML myeloid leukemia cells where it prevents differentiation of factor-dependent myloid progenitors. *See* Knoepfler *et al.*, Oncogene, 20, 5440-5448 (2001).

The evidence described above clearly supports that the claimed nucleic acids have a number of presently available benefit to the public, including: (1) as a diagnostic of AML leukemia cells; (2) modulating expression of Hoxb8; and (3) regulating anteroposterior axis development by targeting Hoxb8. In view of the application providing particular targets of known function for the claimed microRNA-related nucleic acids, Applicant respectfully submits that the specific and substantial utility requires are satisfied in accordance of Fisher and the Guidelines.

(3) Credible Utility

An asserted utility is credible if the assertion is believable to a person of ordinary skill in the art based on the totality of the evidence and reasoning provided. An assertion is credible unless (i) the logic underlying the assertion is seriously flawed, or (ii) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Accordingly, the invention must be operable to achieve useful results. *See Guidelines* at page 5 and *In re Swartz*, 232 F.3d 862 (Fed. Cir. 2000). The proper inquiry for determining credible utility is whether a person of ordinary skill in the art would conclude that the asserted utility is more likely than not true. Applicant respectfully submits that the record clearly shows that one of ordinary skill in the art would believe that the claimed nucleic acids may be used to modulate expression of the specific mRNA targets.

At page 9 of the Office Action, the Examiner asserts that a credible utility is lacking because the Applicant has not presented any evidence or established any nexus that SEQ ID NO: 48 does target and/or inhibit a specific gene much less that the expression or inhibition of expression of SEQ ID NO: 48 may be used to prevent or treat a disease associated with a target sequence. Applicant respectfully disagrees.

As discussed above, Table 4, lines 111 and 122 of the specification demonstrate that the claimed miR (SEQ ID NO: 354) binds to the mRNA of target gene Hoxb8. Applicant further submits that Hoxb8 is recognized in the art as a credible target for trans acting regulatory elements. Specifically, Yekta *et al.* demonstrates that Hoxb8 is a target and is cleaved by hsa-miR-196a, which has only one mismatch at position 12 from the claimed microRNA nucleic acid as set forth in SEQ ID NO: 354 (hsa-miR-196b) and has the same "seed" sequence as SEQ ID NO: 354 (See Yekta *et al.*, *Science* 2004; 304:594-596). miR-196a has a very strong and unusual complementarity to the highly conserved 3' UTR of Hoxb8 (21/22 nts or 90.9%). The claimed

miR (SEQ ID NO: 354, hsa-miR-196b) also has a very high and unusual complementarity to Hoxb8 (20/22 nts or 90.9%). Because the "seed" sequence does not differ from hsa-miR-196a, it is reasonable to assume that the claimed miR (SEQ ID NO: 354; hsa-miR-196b) would bind in the same manner as miR-196a and cleave the mRNA of Hoxb8.

Furthermore, Cohen *et al.* demonstrates that zebrafish dre-miR-196b can repress the translation of HobB8 (See Cohen *et al.*, Endocrinology, 2008;149:1687-96). The zebrafish miR-196b (dre-miR-196b) is only 2 nucleotides different than the claimed human miR sequence (SEQ ID NO: 354, hsa-miR-196b (bolded nucleotides differ).

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hsa-miR-196b      TAGGTAGTTTCCTGTTGTTGGG
dre-miR-196b      TAGGTAGTTTCAAGTTGTTGGG
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These two mismatches do not change the level of complementarity between the claimed human miR sequence and the human target HoxB8 sequence because human HoxB8 and zebrafish HoxB8 are 100% conserved.

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Zebrafish HOXB8 compl. site (5'->3'): CCAACAACAUGAAACUGCCUA
Zebrafish dre-miR-196b (3'->5'):      GGGUUGUUGAACUUUGAUGGAU

Human HOXB8 compl. site (5'->3'):     CCAACAACAUGAAACUGCCUA
Human hsa-miR-196b (3'->5'):        GGGUUGUUGUCCUUUGAUGGAU
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Taken together, human hsa-miR-196a is shown to regulated translation of HoxB8 transcripts from Yekta. Zebrafish dre-miR-196b is shown to regulated translation of zebrafish HoxB8 transcripts from Cohen. The sequence of HoxB8 between humans and zebrafish is 100% conserved. There is only a 1 nucleotide difference between hsa-miR-196a and the claimed hsa-miR-196b sequence (SEQ ID NO: 354) with no differences in sequence over the "seed" sequence. There is only a 2 nucleotide difference between zebrafish dre-miR-196b and the claimed hsa-miR-196b sequence (SEQ ID NO: 354). Accordingly, the claimed miR (SEQ ID NO: 354) would be expected to bind and repress translation of a human HoxB8 transcript. Accordingly, HoxB8 is a credible target for trans-acting elements such as the claimed miRNA.

Furthermore, Applicant asserts paragraph 0181 of the application discloses that the mRNA targets of the claimed polynucleotides were identified as being consistent with the free energy and spatial structure of target binding sites of known miRNAs. The method as described

in paragraph 0180 for identifying target binding sites of miRs is based upon studies at the time of filing demonstrating that miRs bind to target binding sites as disclosed in references such as Wightman *et al.* (1993), Reinhart *et al.* (2000), Slack *et al.* (2000), Lau *et al.* (2001), Lagos-Quintana *et al.* (2001), and Moss *et al.* (1997), which are all cited in the Information Disclosure Statement filed herewith.

In view of the asserted utilities being consistent with the general understanding of miRNAs and their target binding sites at the time of filing and the in vitro demonstration of regulation of the HoxB8 gene by very closely related miRs of the claimed invention, Applicant respectfully submits that one of ordinary skill in the art would believe that each claimed polynucleotide would bind its respective target binding sites. In view of the foregoing remarks, the Applicant respectfully submits that a credible utility is asserted for the claimed polynucleotides.

b. 35 U.S.C. § 112, second paragraph

(1) Claims 17-36

On pages 14-16 of the Office Action, the Examiner rejects claims 17-36 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite.

"comprises … (a) … (b) … (c) … or (d) …"

On page 14, the Examiner asserts that claim 17 is directed to an improper Markush group. Applicant respectfully disagrees. Nevertheless, in view of amended claim 17, which is in the form of "… group consisting of: (a)… (b)… (c)… and… (d)…," Applicant submits that the Markush group in the claim is proper.

"consists of… at least"

On page 14, the Examiner also asserts that the metes and bounds of the limitation "at least" of claim 20 is indefinite in view of the use of this limitation following the term "consists of." Applicant respectfully disagrees. Nevertheless, in order to expedite prosecution of the instant application, this limitation has been removed in amended claim 20 without prejudice to pursuing the subject matter removed from the claim in a continuing application.

"an RNA equivalent"

On page 15, the Examiner asserts that the limitation "an RNA equivalent of" in claims 17 and 20 is unclear in scope and meaning. Applicant respectfully disagrees. Nevertheless, amended claims 17 and 20 recite "a RNA encoded by." Applicant submits that one of skill in the art would

understand that this limitation is related to RNAs that are encoded by the DNA sequences of SEQ ID NOs: 48 and 354 in claims 17 and 20, respectively. For example, one of skill would understand that a RNA can be produced by transcribing a DNA. Accordingly, one of skill would readily interpret the metes and bounds of a RNA encoded by the nucleic acid of claim 17 or 20.

"64/84" and "14/30"

On page 16, the Examiner asserts that the meanings of the limitations "a sequence at least 64/84 identical" and "at least 14/30 complementary" of claims 17 and 20, and claims 27 and 28, respectively, are unclear. Applicant respectfully disagrees. Nevertheless, neither of these limitations is recited in the amended claims.

(2) Claims 18, 23, 25, and 27

On page 15 of the Office Action, the Examiner rejects claims 18, 23, 25, and 27 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. The Examiner asserts that the limitation "the at least 18 nucleotides" of claim 18 does not have sufficient antecedent basis. Applicant respectfully disagrees. Nevertheless, claim 18 has been canceled, thereby rendering moot the rejection of this claim.

In view of the foregoing amendments and remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112, second paragraph.

c. 35 U.S.C. § 112, first paragraph

On pages 16-20 of the Office Action, the Examiner rejects claims 17-36 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. Specifically, the Examiner asserts that the following limitations are not supported in the application as filed: "an isolated nucleic acid consisting of 18 to 120 nucleotides wherein the sequence comprises (a) at least 18 consecutive nucleotides of SEQ ID NO: 48; (b) an RNA equivalent of (a); (c) a sequence at least 64/84 identical to (a) or (b); or (d) the complement of any one of (a)-(c)"; and "the at least 18 nucleotides comprises the sequence of SEQ ID NO: 354."

"nucleic acid consisting of 18 to 120 nucleotides"

On pages 17 and 18, the Examiner asserts that the limitation "nucleic acid consisting of 18 to 120 nucleotides" is not supported by claims 1-3 and paragraph 0015. Applicant respectfully

disagrees. Nevertheless, this limitation has been removed from the amended claims without prejudice to pursuing the removed subject matter in a continuing application.

"at least 18 consecutive nucleotides of SEQ ID NO: 48"

On page 18, the Examiner asserts that neither Table 2 nor paragraph 50905 discloses the limitation "at least 18 consecutive nucleotides of SEQ ID NO: 48" in claim 17. Applicant respectfully disagrees. Nevertheless, this limitation has been removed from the amended claim 17 without prejudice to pursuing the removed subject matter in a continuing application.

"RNA equivalent"

On page 18, the Examiner asserts that neither claim 1 and paragraph 50906 discloses the limitation "RNA equivalent" in claim 17. Applicant respectfully disagrees. Nevertheless, amended claims 17 and 20 recite "a RNA encoded by." Applicant submits that RNAs encoded by SEQ ID NOs: 48 and 354 (GAM7553) are taught in paragraphs 50906-50908 and 50918, which in part recite "GAM7553 precursor RNA folds onto itself, forming GAM7553 folded precursor RNA … which … is typical of *RNA encoded by miRNA genes*" (emphasis added). Accordingly, Applicant submits that one of skill would believe that Applicant was in possession of RNAs encoded by the DNAs of the claimed nucleic acids.

"at least 64/84"

On page 18, the Examiner asserts that neither Table 2 nor paragraph 26993 discloses the limitation "at least 64/84" of claim 17. Applicant respectfully disagrees. Nevertheless, amended claim 17 no longer recites this limitation.

"the complement of any one of (a)-(c)"

On pages 18 and 19, the Examiner asserts that neither claim 1 nor paragraph 50906 discloses the limitation "the complement of any one of (a)-(c)" in claim 17. Applicant respectfully disagrees. Paragraphs 50907, 50908, 50911, and 50912 of the specification as filed discloses the following about the claimed nucleic acids: "first half of the RNA encoded by a miRNA gene is an accurate or partial reverse-complementary sequence of the nucleotide sequence of the second half thereof." Moreover, given the double-stranded nature of nucleic acids and their ability to pair, Applicant submits that the sequence of a nucleic acid inherently teaches its complement. Accordingly, Applicant submits that one of skill would believe that Applicant was in possession of complements of the claimed nucleic acids.

"wherein the at least 18 nucleotides comprises the sequence of SEQ ID NO: 354"

On page 19, the Examiner asserts that neither Table 2 nor paragraph 50907 teaches the limitation "wherein the at least 18 nucleotides comprises the sequence of SEQ ID NO: 354" in claim 18. Applicant respectfully disagrees. Nevertheless, amended claim 18 no longer recites this limitation.

"at least 14/30"

On page 19, the Examiner asserts that Table 4 does not support the limitation "at least 14/30 complementary" of claims 27 and 28. Applicant respectfully disagrees. Nevertheless, this limitation is no longer recited in the amended claims.

"vector" and "probe" comprising "RNA equivalent"

On page 19, the Examiner admits that paragraph 0024 teaches a limitation of a vector including the DNA, but asserts that this paragraph does not teach vectors including "RNA equivalents." On pages 19 and 20, the Examiner similarly admits that the specification teaches a probe comprising the claimed DNAs, but asserts that the specification does not teach probes comprising "RNA equivalents." Applicant respectfully disagrees, but nevertheless, as discussed above, the limitation "RNA equivalent" has been amended to "RNA encoded by" in claims 17 and 20. Applicant submits that as described above, one of skill would believe that Applicant was in possession of a "RNA encoded by" the nucleic acids of claims 17 and 20, and would readily interpret the metes and bounds of such a RNA. Likewise, one of skill would believe that Applicant was in possession of a vector and a probe comprising the nucleic acid of claim 17 or 20 and would readily interpret the metes and bounds of such vectors and probes.

In view of the foregoing amendments and remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112, first paragraph.

d. 35 U.S.C. § 102(b)

(1) In view of NEB

On pages 20-22 of the Office Action, the Examiner rejects claims 17-22, 31, and 32 under 35 U.S.C. § 102(b) under 35 U.S.C. § 102(b) as allegedly being anticipated by Random Primer 24, sold by New England Biolabs in the 1998/99 catalog ("NEB"). The Examiner asserts that NEB teaches a vial containing 9 copies of every possible 24-nucleotide sequence. The Examiner alleges that the specification contains no clear or limiting definition of the term

"isolated" that would clearly preclude isolated mixtures of oligonucleotides of the type sold and disclosed by NEB. Applicant respectfully disagrees and submits that the Examiner's rejection is solely an issue of whether an "isolated" nucleic acid is taught by NEB.

The term "isolated" has a clear meaning to one of skill in the art. As the Examiner notes on page 21, NEB teaches a vial containing over 2.81×10^{14} possible 24-nucleotide sequences. Even if one such tube contained a nucleic acid with the sequence of the claimed nucleic acid, NEB teaches this nucleic acid as only one among 2.81×10^{14} nucleic acids in the vial. One sequence among 2.81×10^{14} is not an isolated nucleic acid. Accordingly, NEB does not specifically teach the sequences of the instantly claimed nucleic acids.

Finally, amended claims 17 and 20 are related to sequences of 22 and 84 nucleotides in length, respectively. In contrast, NEB teaches only 24-mers. Accordingly NEB does not disclose the claimed nucleic acids, and therefore does not teach all the limitations of either amended claim 17 or 20. In view of the foregoing amendments and remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 102(b) in view of NEB.

(2) In view of Fussenegger

On pages 22 and 23, the Examiner rejects claims 17, 20, 31, and 32 under 35 U.S.C. § 102(b) as allegedly being anticipated by US 6,287,813 ("Fussenegger"). The Examiner asserts that Fussenegger teaches an isolated nucleic acid that comprises a sequence that is 79.3% complementary to nucleotides 23-51 of instant SEQ ID NO: 48, and that the Fussenegger nucleic acid meets the structural limitations of the instant claims. In view of amended claim 17, Applicant submits that Fussenegger does not teach or suggest the claimed nucleic acids.

e. Double Patenting

On pages 23 and 24 of the Office Action, the Examiner rejects claims 17-26, 31, and 32 on grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 13 of co-pending U.S. Application No. 11/130,645. The Examiner alleges that nucleic acids related to SEQ ID NOs: 13291 and 3104 of the '645 Application are patentably indistinct from instant SEQ ID NO: 354. The claims of the '645 Application have been amended in a preliminary amendment filed January 17, 2008 to be directed to nucleic acids related to SEQ ID NOs: 4277, 15666, and 15667. *See* Appendix A. Applicant submits that the instant claims are patentably distinct from the amended claims of the '645 Applicant. In view of the foregoing,

Applicant respectfully submits that a double patenting rejection of the instant claims over the claims of the '645 Application would not be appropriate nor applicable at this time.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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Dated: April 15, 2008

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